First Office Action Final Rejection Inappropriate Prosecution History

The present Continued Prosecution Application was filed on February 15, 2001, five months after Applicant received a final rejection from the Examiner. In November, 1999, Applicant responded to a restriction requirement by electing the group of claims directed to GLP-1 crystals and elected the species Val^8-GLP-1(7-37)OH and specifically stated the pages of the Specification wherein the description of this compound is provided.

Later in prosecution, Applicants submitted a declaration which the Examiner considered persuasive and thus, the Examiner withdrew all art rejections. On September 15, 2000, the Examiner issued a Final Rejection, rejecting all claims under the 35 U.S.C. § 112, paragraphs 1 and 2. Briefly, the Examiner asserted that claims relating to the use of a monosaccharide or disaccharide were not adequately described or enabled and that the terms "aqueous," "v/v," and "w/v" make the claims indefinite. Further, in a telephone interview with Applicant's attorney following receipt of that final rejection, the Examiner indicated that the sequence listing was incomplete and that all GLP-1 compounds mentioned in the Specification as well as the claims must have a SEQ ID NO. regardless of whether the name of the compound and/or the actual sequence is provided in the Specification.

Applicants submitted a response to the Examiner's final rejection within two months of receiving the rejection and provided an updated sequence listing and amended the claims to provide the SEQ ID NO: for Val^8-GLP-1(7-37)OH in the claims and addressed the Examiner's section 112 rejections. Applicants then supplemented their response after another phone conservation with the Examiner and provided a claim set incorporating the Examiner's suggestions. Applicants received a one page Advisory action form letter from the Examiner on February 5, 2001. The Advisory action stated that the amendment would not be entered because "The claims drawn to SEQ ID NO:5 [Val^8-GLP-1(7-37)OH] constitute new issues which

would require further search and consideration of patentability." Furthermore, the Examiner stated that the sequence listing was still incomplete and that page 5 of the specification contains "21 sequences which have to meet the Sequence Listing Requirements."

Applicants are not clear as to why the claim amendments that were specifically suggested by the Examiner raise new issues of patentability and require further searching. Applicants have been prosecuting this particular species of GLP-1 exclusively since November of 1999. In addition, although it is not clear to the Applicant why a sequence listing is required for the compounds named on page 5, Applicants complied with the Examiner's request and submitted a sequence listing that provides a sequence for each sequence listed on page 5 as well as throughout the Specification.

So that Applicant could better understand the concerns of the Examiner, this Continued Prosecution Application was filed. In addition, Applicant simultaneously requested an interview in writing with the Examiner. However, the Examiner apparently refused to grant an interview and issued a First Office Action Final Rejection to which this response is directed.

In this Final Rejection, the Examiner again stated that the Sequence Listing is incomplete because the Specification has not been amended to incorporate the SEQ ID Nos. The Examiner also rejected the amended claims under 35 U.S.C. § 112, paragraphs 1 and 2. The Examiner asserted that the Final Rejection is appropriate because the CPA contains claims drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record had they been entered in the earlier application.

Applicants respectfully point out that "[b]efore a final rejection is in order a clear issue should be developed between the examiner and applicant. . . . The applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application. . . . The examiner should never

lose sight of the fact that in every case the applicant is entitled to a full and fair hearing, and that a clear issue between applicant and examiner should be developed, if possible, before appeal." M.P.E.P. § 706.07. Most importantly, the M.P.E.P. provides that **"it would not be proper to make final a first Office action in a continuing or substitute application where that application contains material which was presented in the earlier application after final rejection or closing of prosecution but was denied entry because (A) new issues were raised that required further consideration and/or search, or (B) the issue of new matter was raised."** M.P.E.P. § 706.07(b). Finally, the M.P.E.P. specifically states, "A request for an interview prior to first action on a continuing or substitute application should ordinarily be granted." M.P.E.P. § 706.07(b).

The Examiner refused to enter Applicants' amended claim set after Final Rejection of the parent case because the amendment raised further issues requiring search and patentability. The Examiner, however, never provided the Applicant with any indication as to what issues were raised by the amended claim set and then proceeded to issue a First Office Action Final after Applicants filed their CPA. Applicants respectfully submit that they were not given the opportunity to understand and/or develop issues that will be argued on appeal before the close of prosecution. Further, Applicants' request for an interview was denied which is contrary to the instructions in the M.P.E.P. which provide that an interview should be granted after filing of a continuing application prior to the first office action. Thus, Applicants respectfully request that the Examiner remove the Final Rejection. In addition, if the Examiner feels that issues of patentability still remain, the Examiner should grant Applicant an interview to determine if these issues can be resolved before the case is appealed.

Rejection under 35 U.S.C. § 112 ¶ 1

The Examiner rejected all pending claims under 35 U.S.C. § 112 ¶1 as "containing subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner then asserted that the amended claims constitute New Matter. Finally, the Examiner suggested that the section 112/Mew Matter rejection can be overcome by "a verified showing of the examples in the specification, wherein the results show that the methods would inherently produce the subject matter entered in the claims."

It is unclear to the Applicant what claim limitations the Examiner considers not to have support in the Specification. Further, a rejection under 35 U.S.C. § 112(1) is a separate rejection from one made under the New Matter provision of 35 U.S.C. § 132. Applicant is unclear whether the Examiner is rejecting all of the claims under both sections and if so, what specifically constitutes New Matter and/or is not adequately described in the Specification.

The Examiner has not clearly articulated or provided support for a rejection under any statute and thus, has not met her burden of presenting a prima facie case of unpatentability. As discussed below, the presently pending claim set is fully supported by the specification and presents no new matter.

The United States Court of Appeals for the Federal Circuit has reiterated in numerous cases that the USPTO has the burden of initially making out a prima facie case of unpatentability at which point the burden shifts to the applicant to come forward with evidence or arguments. *See In re Alton,* 76 F.3d 1168, 37 U.S.P.Q .2d 1578 (Fed. Cir. 1996); *In re Oetiker,* 977 F.2d 1443, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). In *Alton*, the Federal Circuit reasoned that "[i]nsofar as the written description requirement is concerned, that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.'" 76 F.3d at 1175 (quoting *In re Wertheim,* 541 F.2d 257, 263 (C.C.P.A. 1976)). The court further noted that if the specification contains a description of the invention but not in identical words as set forth in the claims, "then the examiner or Board, in order to meet the burden of proof, must

provide reasons why one of ordinary skill in the art would not consider the description sufficient." *Id.* "If examination does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." *In re Oetiker*, 977 F.2d at 1445; *See In re Grabiak*, 769 F.2d 729, 226 U.S.P.Q. 870 (Fed. Cir. 1985).

In this case the Examiner has not provided the Applicant with any reasons as to why the claims are not adequately described in the Specification. Basically, the Examiner has asserted, without citing any support, that she is not convinced that the processes described in the Specification produce the crystals claimed which are also described in the Specification. Should the Examiner continue to stand by this assertion, Applicants respectfully request that the Examiner provide reasons as to why the examiner doubts that which the Applicants have provided in the Specification. The M.P.E.P. provides "When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner. Such an affidavit is subject to contradiction or explanation by the affidavits of the applicant and other persons." M.P.E.P. § 2144.03. Applicants have explained the process for making the crystals of the present invention in detail, have provided a description of the crystal morphology, and have provided several working examples wherein crystals falling within the claims are produced. Applicants are not required to verify that which is in the Specification unless the Examiner provides specific reasons supported by a reference or examiner's affidavit.

The pending claims have support throughout the specification as originally filed. For example, the claims have the following support:

1. Val-8-GLP-1(7-37)OH has been replaced with SEQ ID NO:5. Val-8-GLP-1(7-37)OH was the species elected by the Applicant in response to the Examiner's restriction requirement in November of 1999. The

sequence of Val-8-GLP-1(7-37)OH was provided in the specification as originally filed. The sequence of GLP-1(7-37)OH is provided on page 5, line 9 and labeled SEQ ID NO:1. Val-8-GLP-1(7-37)OH is listed on page 5, line 19. The nomenclature is described on page 4, line 31 through p. 5, line 5. The amino terminus is assigned residue 7. Thus, Val-8-GLP-1(7-37)OH is GLP-1(7-37)OH [SEQ ID NO:1] wherein valine is substituted for the wild-type residue at position 8. Furthermore, SEQ ID NO:2 provides a formula for GLP-1 analogs that includes Val-8-GLP-1(7-37)OH [see p. 5, line 25]. The X at position 8 can be Val as well as various other residues. Finally, Example 1 describes the Val-8 species used as "chemically synthesized GLP-1(7-37)OH analog having Val substituted for Ala in position 8 (V8-GLP-1)." See p. 16, line 3.

2. Crystal morphology: On page 10, line 1 the Specification provides "The flat rod shaped or plate-like GLP crystals of the present invention, which are prepared using the claimed process, vary in size and shape to some degree. Generally, they range in size from approximately 2-25 microns (μm) by 10-150 μm and are flat, having a depth of approximately 0.5 to 5 μm." In addition, a number of examples describe the crystals produced in terms of dimension. Example 9 describes the crystals as "40 microns long, 15 microns wide, and 3 microns thick." [p. 22, line 20]. Example 10 described the crystals as "10 to 30 microns long and 10 microns wide." [p. 23, line 22]. Example 13 describes the crystals as "150 μm in length, approximately 25 μm wide and less than 5 μm thick." [p. 25, line 8].

3. Ethanol, propanol, ammonium sulfate, zinc, monosaccharides, and disaccharides:
The concentration ranges of peptide, the pH ranges, the ethanol ranges, the zinc concentration and the ammonium sulfate concentration have basis in the

original claims as filed as well as throughout the rest of the Specification. For example, original process claim 2 provides a peptide concentration of between 1-10 mg/mL and a pH range between 6 and 7. Original process Claim 3 provides zinc in a molar ratio between 0.5 and 1.7 to peptide and a peptide concentration between 1-20 mg/mL as well as a pH range between 7-10. Additional support in the Specification can be found on pages 11-13. The alcohol concentration is stated as ranging from 2-15% (v/v), preferable 3-13%. Ammonium sulfate concentration is provided as approximately 1% (w/v). [p. 11, lines 19-26]. Peptide concentration ranges of 1-20 mg/mL, preferably 2-10 mg/mL are provided and the total zinc as a molar ratio to peptide is provided as 0.5 to 1.7, preferably 0.6 to 1.5. [p. 12, lines 10-17]. The optimal pH ranges are provided as pH 6-7, preferably 6.4 +/- 0.2 (p. 11, lines 15-16) and as pH 7-10, preferably about 7.2 - 9.7 (p. 12, lines 12-13).

There is also support for the use of a genus of monosaccharides and disaccharides to make the crystals of the present invention. There are two specific examples describing in detail crystals made using a monosaccharide and a disaccharide. On page 3, line 18 of the Specification the inventors state that "tetragonal flat rod shaped or plate-like crystals . . . could be reproducibly formed from a mother liquor containing a GLP dissolved in a buffered solution and . . . a mono or disaccharide, over a wide range of pH conditions." On page 12, line 3, the Specification provides that "mono or disaccharides may be substituted for the alcohol in the same ratios on a weight to volume basis." A list of mono and disaccharides suitable for use in making the crystals of the present invention is also provided. Finally, there are two specific examples wherein Val-8-GLP-1 crystals are made using a monosacchardie or disaccharide. Example 9 on page 22 provides a

protocol to make crystals with 5% trehalose (a disaccharide). On line 18, the inventors state that "[a]fter 24 hours V8-GLP-1 crystal clusters and single rectangular crystals were identified." Measurements of these crystals are also provided. Example 10 on page 23 provides a protocol to make crystals with 10% mannitol (a monosaccharide). Measurements of these crystals are also provided.

Rejection under 35 U.S.C. § 112(2)

The Examiner has also rejected Claims 40 and 75 under 35 U.S.C. § 112(2) as being indefinite and improper composition claims. The Examiner asserts that the preamble to a claim does not change the content of the claim. Applicants respectfully disagree. The preamble in this case states exactly what is being claimed. The claim is directed to a composition containing a compound not just a compound.

Case law makes clear that the language in the preamble of a claim may be considered to specifically limit the claim. The standard is generally that "the preamble is not given the effect of a limitation unless it breathes life and meaning into the claim." M.P.E.P. 2111.02; *Kropa v. Robie,* 88 U.S.P.Q. 478 (C.C.P.A. 1951). In this case the claim is directed to a composition which is defined in the Specification as "homogenous compositions of individual tetragonal flat rod shaped or plate-like crystals of GLPs." Specification, p. 13, lines 15-17. The rest of the claim depends on the word "composition" for completeness or understanding.

Composition claims 42 and 76 comprise crystals as well as zinc. On page 4, line 1, the Specification provides: "The crystal compositions of the present invention are pharmaceutically attractive because they are relatively uniform and remain in suspension for a longer period of time than the crystalline clusters or amorphous crystalline suspensions . . . . Most importantly, the crystal compositions of the present invention display extended, uniform, and reproducible pharmacokinetics which can be modulated by adding zinc using conventional crystal soaking

techniques or, alternatively, by including zinc in the crystallization solution." Additional support can be found on p. 13, line 15 wherein it is stated: "the invention provides homogenous compositions of individual tetragonal flat rod shaped or plate-like crystal of GLP's. Prior to the processes herein disclosed and claimed, such compositions could not be achieved." Additional support for the addition of zinc is also provided on p. 13, line 24.

Sequence Listing

The Examiner indicates that the Specification must be amended to refer to a specific SEQ ID NO. when a sequence is discussed. Applicants' preliminary amendment filed with this CPA specifically amended the specification on page 5 to provide SEQ ID NOs. for every compound named. Applicants, however, respectfully point out that merely naming a compound does not necessitate a sequence listing. See 37 C.F.R. § 821. For example, if the specification mentioned the human GLP-1 receptor, it would not be necessary to provide a SEQ ID NO. and a corresponding entry in an attached sequence listing for the human GLP-1 receptor. Nonetheless, Applicants amended the Specification on page 5 to provide SEQ ID Nos. for a list of compound names known in the art in the preliminary amendment filed with the presently pending CPA. Therefore, Applicants assert that the sequence listing and specification meet the requirements as set forth in 37 C.F.R. § 821.

Conclusion

In view of the remarks provided herein above, it is respectfully submitted that the rejections have been overcome. The pending claims are fully supported by the Specification as originally filed and do not add New Matter. Reconsideration and withdrawal of the rejection and passage of the case to allowance are therefore requested.

If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to call Applicants' Attorney at (317)276-0280.

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